A③

ISSN 0021-5198

# THE JAPANESE JOURNAL OF PHARMACOLOGY

Volume 73 Supplement I 1997

**Proceedings**

The 70th Annual Meeting
of The Japanese Pharmacological Society
March 22-25, 1997
Chiba, Japan

Official Publication
of
The Japanese Pharmacological
Society

# The 70th Annual Meeting

March 22-25, 1997

Funabashi, Chiba

**President: Issei Takayanagi**

## Abstracts

Secretariat
Department of Chemical Pharmacology
Toho University School of Pharmaceutical Sciences

## O-133 Pharmacological profile of T-0201, a potent nonpeptide endothelin antagonist, and preferable effects in models of pulmonary hypertension induced by monocrotaline.

Rikako Yamauchi, Tomoko Hoshino, Yoichiro Ban, Hajime Aihara, Kohei Kikkawa, Hideo Yabana, and Sakae Murata, Lead Optimization Research Laboratory, Tanabe Seiyaku Co. Ltd., Saitama, 335, Japan.

We studied the pharmacological profile of T-0201, a new nonpeptide endothelin(ET) receptor antagonist, and the effects of T-0201 in models of pulmonary hypertension.
*In vitro*, T-0201 antagonized the specific binding of 20pM [125I]-ET-1 to human cloned ETA and ETB receptors with Ki values of 15pM and 41nM, respectively. T-0201 showed dose-dependent inhibitions of ET-1-induced contraction n the isolated rat aorta(ETA, pA2=8.9) and of sarafotoxin S6c-induced contraction in the isolated rat trachea(ETB, pA2=6.5). *In vivo*, T-0201 (0.01-10mg/kg, i.v.) inhibited the pressor response to exogenous big ET-1(1nmol/kg, i.v.) in anesthetized rats and dogs.
In dehydromonocrotaline-induced pulmonary hypertensive dogs, intravenous infusion of T-0201 (10μg/kg/min. for 60min.) under anesthesia decreased pulmonary arterial pressure by 20% without changing systemic blood pressure and heart rate. Moreover, in monocrotaline (60mg/kg, s.c.)-treated rats, consecutive administration of T-0201(0.03-0.1mg/kg, p.o., b.i.d.) for 18days dose -dependently inhibited the progression of right ventricular hypertrophy.
Thus, T-0201 is a potent ETA selective antagonist and acute or consecutive administration of T-0201 may be useful for treatment of pulmonary hypertension.

## O-134 Involvement of nitric oxide in endothelin ETB receptor-mediated inhibitory actions on antidiuresis and norepinephrine overflow induced by stimulation of renal nerves in anesthetized dogs.

Gen Matsuo, Yasuo Matsumura, Kiyoshi Tadano, Takashi Hashimoto and Shiro Morimoto. Department of Pharmacology, Osaka University of Pharmaceutical Sciences, Takatsuki, Osaka 569-11, Japan.

We examined the effect of sarafotoxin S6c (S6c), a selective endothelin (ET) $ET_B$ receptor agonist, on renal actions and norepinephrine (NE) overflow induced by renal nerve stimulation (RNS) in anesthetized dogs, with or without blockade of an endogenous nitric oxide (NO) generation by $N^G$-nitro-L-arginine (NOARG), a NO synthase inhibitor. RNS (0.5-2.0 Hz) produced significant decreases in urine flow (UF), urinary excretion of sodium ($U_{Na}V$) and fractional excretion of sodium ($FE_{Na}$), and increased NE secretion rate (NESR), without affecting systemic and renal hemodynamics. When S6c (1 ng/kg/min) was infused intrarenally, there was a slight and transient increase in renal blood flow (RBF), without any change in systemic hemodynamics, and this response was followed by gradual reduction. Basal level of UF was increased by the peptide infusion without effects on $U_{Na}V$ and $FE_{Na}$. In addition, S6c administration elicited an increase in urinary excretion of NO metabolites ($U_{NOx}V$), $NO_2^-$ and $NO_3^-$. During S6c infusion, RNS-induced antidiuretic action and increase in NESR were significantly attenuated. RNS during intrarenal arterial infusion of NOARG (40 μg/kg/min) caused potent reductions in urine formation, and decreased RBF and glomerular filtration rate. Simultaneously, NESR was markedly increased. In the presence of NOARG, S6c-induced suppressive actions on reductions in urine formation and increase in NESR in response to RNS were markedly attenuated. The peptide could not increase $U_{NO_3}V$. These findings suggest that ET functions as an inhibitory modulator of renal noradrenergic neurotransmission through $ET_B$ receptor mechanisms, which may be due to the peptide-induced NO production.

## O-135 Involvement of tyrosine kinase in pressure-induced contraction of rat cerebral artery.

Naohiro Masumoto, Koichi Nakayama, Akihiro Oyabe, Mayumi Uchino, Kunio Ishii, Kazuo Obara and Yoshiyuki Tanabe. Department of Pharmacology, Faculty of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka City, Shizuoka 422, JAPAN.

In order to determine whether protein tyrosine kinase mechanisms are involved in pressure-induced contraction, we compared effects of three structurally-unrelated tyrosine kinase inhibitors and orthovanadate, a tyrosine phosphatase inhibitor, on the pressure-induced contraction of the posterior cerebral artery isolated from rats. Herbimycin A inhibited the pressure-induced contraction, while it only slightly inhibited contractions produced by KCl or U46619, a thromboxane $A_2$ analogue. Genistein inhibited not only the pressure-induced contraction but also the U46619-induced one. Tyrphostin 23 significantly attenuated contractions in response to three different stimuli, i.e., pressure, KCl, and U46619. Orthovanadate potentiated the pressure-induced contraction, and the potentiation was effectively inhibited by pretreatment for 20 min with herbimycin A or genistein. These results suggest that herbimycin A is the most specific and potent inhibitor of the pressure-induced contraction and that a protein tyrosine kinase mechanism may play an important role in the genesis of the pressure-induced contraction of the rat cerebral artery.

## O-136 Signal transduction pathways toward pre- and posttranscriptional regulations involved in interleukin 1 receptor-triggered induction of nitric oxide synthase in vascular smooth muscle cells.

Tetsuhiro Hisayama, Toshiyuki Iseki, Seizi Mizutari and Hideki Moritoki. Department of Pharmacology, Faculty of Pharmaceutical Sciences, University of Tokushima, Shomachi, Tokushima 770, JAPAN.

By measuring interleukin 1β (IL-1β)-induced nitrite production in cultured rat aortic smooth muscle cells, we reported possibilities that novel protein kinase C (nPKC) is involved in expression of inducible nitric oxide synthase (iNOS), and that a prolonged activation of the IL-1 receptors until the posttranscriptional stage is necessary for the induction process. To explore these possibilities, IL-1 receptor-triggered signal transduction pathways leading to the iNOS induction have been studied with regard to iNOS mRNA production and its degradation. The production of iNOS mRNA by IL-1β was abolished by H-7 and Ro-31-8220 (nonselective PKC inhibitors), and calphostin C (an inhibitor of conventional and novel PKC's), but not inhibited by Gö 6976 (a conventional PKC inhibitor). After iNOS mRNA was produced by IL-1β, transcription was blocked by addition of actinomycin D with and without (control) IL-1 receptor antagonist (IL-1ra), and the mRNA levels in the cells were then chased. IL-1ra increased the rate of loss of the mRNA. Results suggest that IL-1 receptor activation induces iNOS by at least two independent mechanisms; one relates to iNOS gene expression through a nPKC-dependent pathway and the other suppression of mRNA degradation. Simultaneous activation of both pathways may be required for induction of iNOS in cultured rat aortic smooth muscle cells.